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Enantioselective Catalysis for Agrochemicals: Synthetic Routes to (*S*)-Metolachlor, (*R*)-Metalaxyl and (α*S*,3*R*)-Clozylacon

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Abstract: The application of enantioselective catalytic methods for the technical preparation of chiral agrochemicals is illustrated for three active ingredients of the acylanilide type. The key step for the technical synthesis of the herbicide (*S*)-metolachlor is the enantioselective hydrogenation of an imine intermediate using a novel iridium ferrocenyldiphosphine catalyst with an unprecedented high activity and 80% ee. (*R*)-metalaxyl and (α*S*,3*R*)-clozylacon were synthesized via the enantioselective hydrogenation of corresponding enamide precursors with Rh and Ru/binap catalysts with >95% and 99% enantiomeric purity, respectively. © 1998 Society of Chemical Industry

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Key words: Chiral acyl anilides; chiral switch; enantioselective hydrogenation; (*R*)-metalaxyl; (*S*)-metolachlor; (α*S*, 3*R*)-clozylacon

1 Introduction

The biological properties of chiral agrochemicals are often strongly related to the absolute configuration.[1] As a consequence, the technical synthesis of pure or enriched enantiomers is of growing importance in the modern agrochemical industry. A promising technology for very efficient asymmetric syntheses is the application of chiral catalysts but, in the end, the best overall synthesis will be chosen for commercial production. For a technically feasible catalytic process, high enantioselectivity is not the only prerequisite; other factors such as catalyst productivity, catalyst activity, catalyst stability, availability and quality of the starting material, etc., can be even more important from a production point of view.[2] Catalyst productivity, expressed

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as turnover number (ton), determines the catalyst costs. The catalyst activity, given as average turnover frequency for high conversion (tof), determines the production capacity of existing equipment. As a rule of thumb, ton values for large-scale products should be in the order of $2–5 \times 10^4$ and tof values should be $>2 \times 10^3\ h^{-1}$. In the case of smaller volumes and/or more expensive products, the numbers can be somewhat lower. In this contribution, the development of industrially feasible enantioselective catalytic processes for the synthesis of chiral intermediates for (*S*)-metolachlor, (*R*)-metalaxyl and (α*S*,3*R*)-clozylacon is summarized.

2 *Background*

Metolachlor ('Dual' Fig. 1) is one of the most important grass herbicides for use in maize. It is an *N*-chloroacetylated, *N*-alkoxyalkylated ortho-disubstituted aniline. The commercial product exists as a mixture of four stereoisomers, but about 95% of the herbicidal activity is due to the two (1*S*)-diastereomers.[3] As a consequence, Dual Magnum® with (*S*)-metolachlor of 80% enantiomeric purity, introduced in 1997, has the same biological effect as the original commercial product with about 35% less environmental load.

Clozylacon (CGA 80000; Fig. 2, **2**) is a fungicide especially well suited for soil application against oomycetes.[1] Four stereoisomers exist because of the stereogenic centre and the atropisomerism due to hindered rotation around the carbon–nitrogen bond. The desired fungicidal activity arises mainly from the isomer with the absolute configuration α*S*,3*R*.

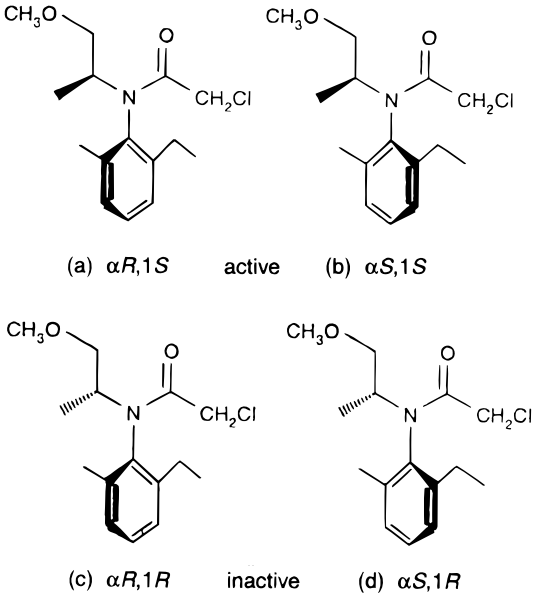

Fig. 1. Stereoisomers of metolachlor.

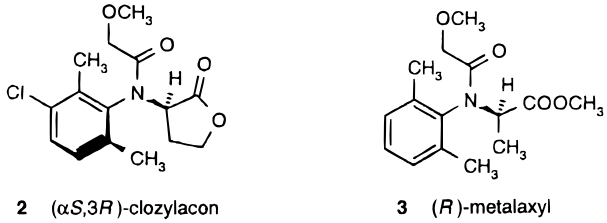

Fig. 2. Structures of clozylacon and metalaxyl.

Unlike other fungicides racemic metalaxyl (Ridomil®) showed no phytotoxic effects against crop plants when applied for the control of *Phytophthora infestans* (Mont.) de Bary and *Pythium ultimum* (Trow.), and therefore separation of the individual enantiomers is not absolutely necessary.[1] However, because the (*R*)-enantiomer is responsible for all of the fungicidal activity, the application of enriched (*R*)-metalaxyl (Ridomil Gold®; Fig. 2, **3**) is advantageous from an ecological point of view.

3 *Approaches and results*

3.1 (S)-*Metolachlor.* Two approaches for the enantioselective synthesis of (*S*)-metolachlor were investigated in some detail:

i. The hydrogenation of the MEA enamide precursor (Fig. 3, **4**) of metolachlor by analogy to the L-dopa process of Monsanto. However, all attempts to hydrogenate the three isomeric MEA enamides failed.
ii. The enantioselective hydrogenation of *N*-(2-ethyl-6-methylphenyl)-*N*-(1′-methoxymethyl)-ethylideneamine (MEA imine; Fig. 3, **5**) turned out to be very difficult.[4] The following catalyst parameters proved to be important: the metal, the type of the diphosphine, addition of halide ions and the presence of an acid; in addition, pressure and temperature also strongly influenced the catalyst activity.

With hydrogen at 80 bar and 50°C, using a catalyst generated *in situ* from $[Ir(cod)Cl]_2$ and the ferrocenyldiphosphine ligand, xyliphos (Fig. 3., **6**) (R = 3,5-xylyl, R′ = Ph) and with a substrate-to-catalyst ratio of 1×10^6, complete conversion was reached within 2–3 h with an initial tof exceeding $1{\cdot}8 \times 10^6\ h^{-1}$. The best ees were >80%. A production process was developed that has been in operation since the end of 1996.

3.2 (αS,3R)-*Clozylacon.* Clozylacon was synthesized successfully via asymmetric hydrogenation of the enamide I (Fig. 3, **7**) followed by chlorination to yield a mixture of the two atropisomers (α*S*,3*R*)- and (α*R*,3*R*)-clozylacon, which were separated by crystallization. Best overall results for the catalytic hydrogenation were obtained with a Ru-binap catalyst (Fig. 3, **8**; 66% ee, 4000 turnovers at 100 bar and 50°C). Enantiomerically pure hydrogenation product was isolated in 63% chemical yield by a single crystallization of the crude reaction mixture.[5]

3.3 (R)-*Metalaxyl.* The key step for the enantioselective synthesis of (*R*)-metalaxyl was the enantioselective

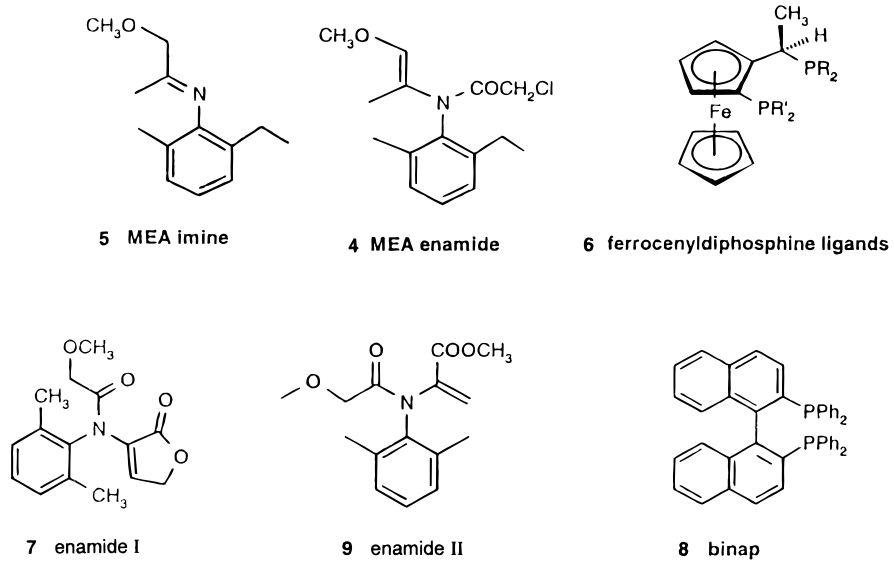

Fig. 3. Structures of intermediates and catalysts mentioned in text.

hydrogenation of the enamide II (Fig. 3, **9**). Of 34 chiral Rh diphosphine catalysts tested, 12 produced ees >90% but most showed low activity. Optimization and scale-up experiments were done with the catalyst $[Rh(nbd)_2]BF_4$/(R,R)-Me-duphos. With hydrogen at 10 bar and 60°C, and with a substrate-to-catalyst ratio of 5×10^4, 95·6% ee and a turnover frequency of $5{\cdot}2 \times 10^3\ h^{-1}$ were obtained, well above the specified minimum limits. The alternative route via enantioselective hydrogenation of the corresponding imine turned out not to be feasible.

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Synthesis and Insecticidal Evaluation of Imidacloprid Analogs

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Abstract: Imidacloprid analogues containing a nitroalkylidene instead of a nitroguanidine unit have been prepared and evaluated for investigation as potential insecticides. No nitroalkylidene analogue showed significant activity against the test insects. © 1998 Society of Chemical Industry

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Key words: imidacloprid; insecticide; α-nitroalkene

1 Introduction

Imidacloprid (Fig. 1; **1**) is a systemic neonicotinoid[1] insecticide discovered by Bayer.[2] It controls a broad range of commercially important pests such as soil and sucking insects and termites and is used as seed dressing, as a soil treatment and as a foliar treatment in such

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